

REMARKS

I. Status of the Claims

Claims 1-40 were filed with the initial application. Claims 2, 3, 5-8 and 10-40 were later withdrawn from consideration. Thus, claims 1, 4 and 9 are under consideration, have been examined and stand rejected.

II. Rejections Under 35 U.S.C. §112, First Paragraph (Written Description)

The examiner has again maintained the written description rejection under 35 U.S.C. §112, first paragraph, alleging that there is a lack of a clear description of small molecule inhibitors of NF-AT3. The examiner again cites to the *Lilly* case for the proposition that “an adequate written description of a DNA requires a precise definition.” Applicants submit that examiner is attempting to create a rule of law from *Lilly* where none currently exists. *Lilly* and its subsequent cases have **not** required that an invention must **always** be specifically described as *Lilly* required for those **particular** DNA molecules, nor do the cases require that a genus must be described in its entirety, but rather that a genus may be claimed from a representative number of contained species.

Recent cases elaborating on the holdings of *Lilly* show that “the failure of the patent to describe the claimed sequences by anything other than their function” is problematic, but that the proper standard varies depending on the invention and whether it can be described in more than a functional way. See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 285 F.3d 1013 (Fed. Cir. 2002). Both *Lilly* and *Enzo* require that “the disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter of the claim.” The important point of both cases is that function alone, *i.e.*, wishful thinking, cannot support a set of claims to the molecules (or

DNA) behind that function. However, it does not set up a proscription against the generic claiming of biological molecules. In this regard, it is thus of utmost importance to note that the present specification does not rely on function alone; specific examples and specific molecules are given so that one of skill in the art would be able to visualize or recognize the subject matter of the claims.

The examiner asserts that configuration of the second zinc finger of GATA4 is not known and that specific structures are not disclosed in the application for GATA4 mimetics, antisense molecules, or competitive inhibitors of NF-AT3, and that such lack of knowledge also somehow constitutes a failure of written description. Knowledge of the actual binding sites and exhaustive listings of structures are *not* a requirement for one of skill in the art to appreciate that inventors had possession of the claimed invention. Moreover, as discussed in the declaration of Dr. Rick Gorczynski, those of skill in the art would not doubt that GATA4 does indeed bind to NF-AT3, nor would they challenge the notion that interference with that interaction will have inhibitory effects on NF-AT3's ability to activate gene transcription of hypertrophic genes, such interference clearly being mediated by any of the molecules or agents listed above or referenced in the specification.

As stated in MPEP §2163, an "objective [of §112] is to put the public in possession of what the applicant claims as the invention." Applicants submit that, unlike the *Lilly* case, where the DNA molecules at issue had not yet been discovered, a number of the NF-AT3 targeting molecules disclosed by applicants *are already known*, and thus have been sufficiently described to put the public in possession of the invention. This provides yet another important distinction between the instant application and *Lilly*, to which the examiner repeatedly points.

The written description requirement does not demand exhaustive listings of molecules and detailed description of binding sites and binding regions. Applicants again cite to *Lilly*, which states “a specification may, within the meaning of §112 P1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.” This specification goes beyond simply claiming an undescribed molecule, it actually refers to GATA4 mimetics, DTC’s, antisense molecules (p. 27, lines 12-20), antibodies, competitive inhibitors of NF-AT3 (p. 30, line 21) as well as other proteins that inhibit NF-AT3 (in addition to Examples 3, 6-9, see Summary of the Invention page 4, lines 15-25). These examples describe specific molecules known in the art and whose mention alone should be sufficient to satisfy the written description requirements of §112.

Furthermore, the examiner complains that antibodies and mimetics are described in a functional way and without detailed description of the actual binding sites. Just as above, applicants note that the examiner appears to be overextending the description requirements of *Lilly*. The specification describes specific molecules that interact with NF-AT3 in a way that goes beyond mere wishful thinking. The examiner argues that “the structure of the claimed GATA4 mimetics, [and] antisense molecules” are not disclosed. However, these molecules are defined by the prior art structures of the target molecules, and their absence from the specification is of no significance.

Further, these molecules are shown to interact, or can be proven with little experimentation to interact, with NF-AT3. That alone is sufficient to describe the invention in a comprehensible way to the public. The mere fact that they are not described atom by atom does not rob the claims of written description. The examiner also notes that the inhibitors have “no

common structural attributes.” However, applicants were unaware that commonality of structure is required for claiming a genus of inhibitors.

The above statements, taken in light of *Lilly* and *Enzo* as those courts intended, should successfully traverse the Examiner’s rejections for lack of written description. Therefore, Applicants argue that this rejection should rightfully be withdrawn.

III. Rejection Under 35 U.S.C. §112, First Paragraph (Scope)

Claims 1, 4 and 9 are “newly” rejected for allegedly excessive “scope” under §112, first paragraph, although the rejection is a mere reiteration of the prior enablement rejection. The examiner has apparently rejected all of applicants’ prior arguments, and still argues that the art is unpredictable, that the invention has not been enabled by the specification, and that it would constitute “an undue burden” for one of skill in the art to practice the invention. Applicants respectfully traverse this rejection and reiterate that the examiner has misapplied the standard of undue experimentation.

It may be true that the use of NF-AT3 inhibitors to treat hypertrophy is not well-known, but the information provided in the specification, coupled with what was known prior to this invention, would allow one of skill in the art to practice the invention. The examiner’s criticism almost seems to rise to the level of requiring a working model, and according to MPEP §2164.02 “an applicant need not have actually reduced the invention to practice prior to filing.” It is important to remember that “because only an enabling disclosure is required, applicant need not describe all actual embodiments. The absence of working examples will not by itself render the invention non-enabled. Furthermore, a single working example in the specification for a claimed invention is enough to preclude a rejection which states that nothing is enabled.” MPEP

§2164.02. Examples 6 through 9 clearly show *in vivo* proof that use of NF-AT3 inhibitors can be a method to treat hypertrophy.

The examiner has rejected experimental data in the application by asserting that the transfected cells and transgenic mice are not representative of what would be found in human subjects and, thus, that the data are not enabling for *in vivo* use in patients. The examiner has further rejected the experimental data because he claims that no one specific example puts together all the teachings of the specification. That is not a requirement of the laws of patents and goes far beyond any currently accepted enablement or “scope” standards. Applicants refer to the affidavit of Dr. Rick Gorczynski, regarding the validity of the transfection model and transgenic mouse model. In particular, Ritter *et al.*, *Circulation*, 105:2265-2269 (2002), showed that NF-AT2 is indeed in a dephosphorylated and therefore more active form in hypertrophic heart, as compared to normal human heart. These results provide *in vivo* evidence from a human clinical setting, albeit indirect, that there is an altered NF-AT phosphorylation state in hypertrophied myocardium. It further validates the notion of targeting NF-ATs therapeutically to combat hypertrophy by interfering with the NF-AT transcriptional cascade.

Regarding the issue with transfected cells, applicants refer to the publications of Molkenstein, J. “The Zinc Finger-containing Transcription Factors GATA-4, -5, and -6” (*J. Biol. Chem.* 275:50, 38949-38952, 2000), and Olson *et al.* “Remodeling muscles with calcineurin,” (*BioEssays* 22:510-519, 2000). Based on the results set forth in these manuscripts, it is clear that a person of ordinary skill in the art would recognize that NF-AT3 does indeed interact with GATA-4, which also abrogates the Examiner’s problems with the specification not disclosing “the configuration of the second zinc finger of GATA4 or the C-terminal portion of NF-AT3,” which, he claims, makes determining their binding unpredictable. The actual data and the

references cited argue exactly the contrary to this point. Perhaps the best information on this subject comes from the Molkentin mini-review, which summarizes the state of the art as of over two years ago. This article states “GATA-4 also physically interacts by way of the C-terminal zinc finger with nuclear factor of activated T-cells-c4 (NFAT).” (p. 38951, also see Molkentin, *Cell* 93, 215; and Morin, *EMBO J.*, 19, 2046). What this review article makes clear is that the field of cardiac hypertrophy studies accepts that GATA-4 does indeed interact with NF-AT3. See also the Gorczynski Declaration.

Applicants further submit that this rejection goes beyond any reasonable enablement requirements for §112. Applicants refer to *In re Robins*, 429 F.2d 452 (CCPA 1970) cited by *Lilly*, stating, “Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct.” Furthermore, *Robins* holds that a “specification which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement ... unless there is reason to doubt the objective truth of the statements therein.” The *Robins* court also demands that “Section 112 requires nothing more than objective enablement. How such teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.”

The examiner has also repeatedly stated that one of skill in the art would not know how to make and use the claimed method, using the small molecule single chain antibodies. He instead argues for yet another exhaustive listing of antibody structure and function, which is a standard that runs contrary to law. *In re Wands*, 858 F.2d at 737 (Fed. Cir. 1988), states that so long as there is “considerable guidance” in the specification and “all of the methods to practice the invention [are] known,” then “it would not require undue experimentation to obtain

antibodies needed to practice the claimed invention.” While more enablement may be required where the art is unpredictable, there is no *per se* rule for a working model. The invention must simply enable one of skill in the art to practice that invention, and there is nothing contained in the current application that goes beyond the capabilities of one of skill in the art (MPEP §2164.01 - “the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.”). Also instructive is *U.S. v. Telectronics, Inc.* 857 F.2d 778 (Fed. Cir. 1992), that “a patent need not teach, and preferably omits, what is well known in the art ... the test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art.”

Furthermore, the Examiner now asserts that the entire field of anti-sense technology was unpredictable and unreliable as of the time of filing. He uses as his proof of point a reference from 1995 by Gura (*Science*, 1995, 270:575-577), even though the application was filed in 1998. As such, Applicants refer to Bennett (*Biochem. Pharmacol.*, 1998, 55(1):9-19) which states first that “antisense oligonucleotides are widely used as tools to explore the pharmacological effects of inhibiting expression of a selected gene product,” and even more importantly, that “with careful selection, proper controls, and careful dose-response curves it is possible to utilize antisense oligonucleotides as effective research tools and potentially as therapeutic agents.” These statements, made at the time of filing, directly contradict the statements of Gura, made 3 years before filing, that the Examiner uses to prove that antisense technology is and was unpredictable.

Though applicants have made these arguments previously, and though these apply with considerable force to the allegedly new “scope” rejection, the examiner has not addressed them.

Applicants reassert that the discussion above shows that the specification does, in fact, enable one of skill in the art to practice the claimed invention. Therefore, it is respectfully requested that the claims be reconsidered and the rejection be withdrawn.

IV. Rejection Under 35 U.S.C. §102

Claim 1 was again rejected by the examiner under 35 U.S.C. §102(b) as allegedly being anticipated by Haverich *et al.*, Ried *et al.*, McCaffrey *et al.*, and Martinez-Martinez *et al.* Applicants have asserted before and restate that for literal anticipation of a claim, “a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter.” *PPG Industries Inc. v. Guardian Industries Corp.*, 37 USPQ.2d 1618, 1624 (Fed. Cir. 1996).

Applicants assert that every element in claim 1 is not found in any of the prior art references. Claim 1 teaches treatment of *hypertrophy* by inhibiting the function of NF-AT3 in a cardiomyocyte using a compound that inhibits the function of NF-AT3. The Haverich and Reid references teach the use of cyclosporin A (CsA) for treatment of transplantation disease; they do *not* teach, much less suggest treatment of hypertrophy or effects on cardiac structure. They are instead directed towards improving cardiac *function* in a post-transplant environment. Additionally, while the McCaffrey and Martinez-Martinez references *do* teach that CsA is an NF-AT3 inhibitor, they do not teach the use of an NF-AT3 inhibiting compound to treat hypertrophy. Not one of these references teaches the invention, nor do the collection of them inherently predict or assert the invention.

The Examiner points to *Ex parte Novitski* to support an inherency argument, and argues that applicants have not addressed this citation. This is untrue. *Novitski* merely states that

inherent anticipation may lie, that claims are interpreted as broadly as reasonably possible, and that limitations are not read into the claims. However, a limitation of the instant claims is treating cardiac hypertrophy. Thus, nothing must be read into the claims, and the claims cannot be read to *exclude* this limitation.

As pointed out before, applicants submit that the case law requires that an inherent disclosure “must be certain.” *Ex parte McQueen*, 123 USPQ 37 (Bd. App. 1958). There is no evidence from the cited references that hypertrophy had been treated or even analyzed. The prior art specifically deals with transplantation disease and cardiac function after transplant in response to CsA application. Transplantation disease has not and is not defined as cardiac hypertrophy, and it is possible to have one without the other, thus, there cannot be any inherency. The references do not teach a treatment for hypertrophy nor would one of skill in the art be expected to infer from these references that CsA, and subsequently NF-AT3 inhibitors, were being used to treat hypertrophy. The examiner has not even attempted to address this issue, instead merely repeating the previous rejection.

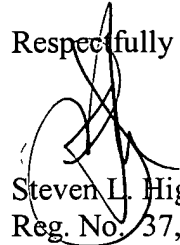
Thus, again, applicants submit that in the absence of an indication that cardiac hypertrophy *was* in fact treated in the work described by the cited references, the rejection cannot be certain and therefore fails to meet the standards required for an inherency rejection under 35 U.S.C. §102(b). Applicants therefore respectfully request that the rejection under §102(b) be withdrawn.

V. Conclusion

Thus, applicants respectfully request, in the interest of conserving time, applicants’ finances and the PTO’s resources, that the examiner be forced to raise these new rejections in the

context of the appeal. Should any interested person believe that further discussion of this matter is required, a call to the undersigned attorney at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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Date: October 23, 2002